Chapter 2
Liver Injury, Inflammation, Repair, and Fibrosis

A1a. Identify individual liver cell type-specific responses to inflammatory mediators. Multiple publications have documented liver cell responses to cytokines, chemokines, adipokines and growth factors including PDGF-C (Campbell JS. *PNAS* 2005;102:3389), leptin and adiponectin (Ding X. *Am J Pathol* 2005;166:1655), angiotensin, TGFβ and others. (20%)

A1b. Elucidate whether and how nutritional factors affect liver cytotoxic and fibrotic pathways. Numerous studies have identified how dietary fat results in NF-κB activation in both hepatocytes and Kupffer cells (Dela Pena A. *Gastroenterology* 2005; 129:1663; She H. *J Biol Chem* 2005;280:4959). (10%)

A2a. Define the role of anti-apoptotic therapy in liver injury, fibrosis, and regeneration. Apoptosis is the underlying mechanism of hepatocyte cell death in many liver diseases, and its inhibition results in lessening of injury and acceleration of recovery in some animal models. Caspase inhibitors have been developed for this purpose that are now in phase I/II trials in humans (Linton SD. *J Med Chem* 2005; 48:6779). (10%)

A2b. Identify the impact of individual leukocyte sub-populations and their mediators on liver injury, fibrosis, and regeneration. Recent research indicates that T- and B-lymphocytes and macrophages, all contribute to hepatic fibrosis, probably mediated by their effects on hepatic stellate cells (Novobrantseva TI. *J Clin Invest* 2005;115:3072). (10%)

A3. Develop noninvasive biomarkers for fibrosis. A variety of serum panels with potential biomarkers as well as noninvasive imaging techniques (such as elastography) for assessing hepatic fibrosis have been described, but none have been widely accepted. This area of research is encouraged through the following program announcements: "Development of Disease Biomarkers" (PA-05-098) and "Noninvasive Methods for Diagnosis and Progression of Diseases" (PA-04-088). (10%)

B1. Identify individual liver cell type-specific extrinsic (e.g., mediator-based) and intrinsic (e.g., organelle-based) cytotoxic signaling pathways. Progress has been made in identifying several cytotoxic signaling pathways that lead to liver cell apoptosis, but the relative role and interactions of these pathways needs further elucidation, particularly in humans (Reinehr R. *J Biol Chem* 2005;280: 27179; Klein C. *J Clin Invest* 2005;115:860; Guicciardi ME. *Gastroenterology* 2005;129:269.) (10%)

B2a. Identify the integrative mechanisms mediating oxidative, nitrosative, hypoxic, and ischemic-reperfusion injury and the role of sinusoidal cells. The integrative mechanisms modulating oxidative, nitrosative, hypoxic and ischemic injury of endothelial cells still remains unclear. The NIH encourages research into the mechanisms of various types of liver injury through initiatives on "Mechanisms of Alcoholic Hepatitis" (PA-02-078), "Preventing Mitochondrial

Stress in Diabetes and Obesity" (RFA-DK-05-005), and "Ubiquitin and Ubiquitin-like Modifications Regulating Disease Processes" (PA-03-145). (0%)

B2b. Identify the proteomic response of the liver and liver-derived serum proteins as intermediate biomarkers for liver disease progression and response to therapy. The proteomic response during disease progression and with therapy of liver disease are the topic of intensive investigation. The NIH encourages research in proteomics of the liver in the program announcement PA-04-81 ("Proteomics: Diabetes, Obesity, and Endocrine, Digestive, Kidney, Urologic, and Hematologic Diseases"). (0%)

B3. Develop gene-, cell-, or pharmacology-based therapies for hepatic injury. Modulators of the activity of nuclear receptors (FXR, PSR, CAR, PPARα and PPARγ) are being developed and evaluated as therapies for liver disease. The role of the thiazolidinediones (PPARγ agonists) in therapy for chronic hepatitis C and NASH is being actively pursued in several NIH-funded trials. (10%)

C1. Develop relevant and robust animal models of hepatic injury, inflammation, and fibrosis progression and resolution. The NIH encourages development of relevant animal models through its initiative on "Animal Models of NIDDK-relevant Diseases" (PA-05-049). The *mdr* knockout mouse develops biliary inflammation and fibrosis that resembles primary sclerosing cholangitis in humans (Popov Y. *J Hepatology* 2005;43:1045). (10%)

C2a. Using high-throughput screens, identify candidate small molecules that modify cytotoxic and fibrotic pathways in liver cells. Progress in this area will require development of methods for screening small molecules that augment or impede cell signaling pathways related to apoptosis and fibrosis. This area is the focus of NIH Roadmap initiatives, including the RFA "Pilot-Scale Libraries for High-Throughput Drug Screening" (RFA-RM-05-014) and a PA "Development of Assays for High-Throughput Drug Screening" (PA-05-068). (0%)

C2b. Define genetic determinants of disease risk and progression in acute/ chronic liver injury, fibrosis, and regeneration. Genetic determinants of hepatic fibrosis are being intensively examined in cohorts of patients with various liver diseases. Genes associated with increased risk of disease progression include complement factor 5 (Hillebrandt S. *Nat Genet* 2005;37:835). Additional genes under scrutiny include TGFβ, IFNγ, IL-10, Mx1, PKR and angiotensinogen. (10%)

C3. Develop mechanism-based drug therapy in fibrotic disease, targeting pro-fibrogenic and fibrosis resolution pathways. Both industry- and NIH-funded investigator-initiated research programs are active in this area. Approaches currently being evaluated in animal models include inhibitors of: angiotensin II, endothelin, TGFβ signaling, cannabinoid receptors, and stellate cell activation. (0%)

Figure 4. Estimated Progress on Liver Injury, Inflammation, Repair, and Fibrosis Research Goals, 2005 (Year 1)